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BY HAND DELIVERY

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

AMENDMENT TO CITIZEN PETITION
(Docket No. 2004P-0061/CP 1)

The undersigned, on behalf of Jerome Stevens Pharmaceuticals, Inc. (JSP), submits this amendment to a petition dated February 10, 2004 filed under § 505 of the Federal Food, Drug and Cosmetic Act (FDCA) and 21 C.F.R. §§ 10.25 and 10.30. This amendment supplements information provided in the February 10, 2004 petition and is meant to be cumulative and not to substitute or delete any of that prior information. JSP requests that the Commissioner of the Food and Drug Administration (FDA) revoke the generic drug approval granted to Mylan Pharmaceuticals, Inc. (Mylan) for levothyroxine sodium (ANDA 76-187) as therapeutically equivalent to Unithroid because the approval was based on a pre-NDA sample of Unithroid.

This petition raises an issue that is important for public health. Levothyroxine is the leading treatment for hypothyroidism and the management of thyroid cancer. It is prescribed annually to more than 13 million Americans (nearly 1 out of every 19). The drug is safe and effective only when administered in precise doses and when manufactured consistently and within specific potency ranges. FDA documented that manufacturing processes vary with significant variability between drug-makers and product lots. *See* 62 Fed. Reg. 43,535 (Aug. 14, 1997). This variability can include use of manufacturing overages and stability overages. A small and unexpected difference in potency may present a serious health hazard in patients with coronary heart disease, cancer, and in pediatric patients. Neither the patients who depend on these drugs, nor the clinicians who prescribe them, can risk the uncertainty of receiving a generic substitute that is not manufactured with the same degree of consistency and accuracy as the reference listed drug.

FDA has taken the position with JSP that a generic comparison requires both pharmaceutical equivalence and bioequivalence of two drug products in order to obtain an AB

2004P-0061 AMD 1

rating between those two drug products.[1] The Agency noted in its January 23, 2004 meeting with JSP that "pharmaceutical equivalence requires, among other things, a demonstration that the test and reference products contain the same amount of drug substance and that the two products are the same dosage form."[2] It noted that pre-approval batches of Synthroid, for example, were released with a stability overage and that this overage draws into question whether the two products are pharmaceutical equivalents, even if the potency of active ingredient were the same when tested.

Finally, the Agency cited its regulations related to the conduct of in vivo bioequivalency studies.[3] These regulations, in the view of the Agency, require use of an "appropriate reference material." During the January 23, 2004 meeting with Dr. John Jenkins, he made it clear that the Agency interprets this term as requiring that the reference material is "taken from a current batch of a drug product that is the subject of an approved new drug application and that contains the same active drug ingredient or therapeutic moiety."[4]

Like Synthoid, Unithroid is often also made with an overage (in manufacturing), although not a stability overage of the size reportedly included in pre- and post-NDA Synthroid. Each lot differs in potency within the range accepted by the United States Pharmacopoeia (USP).[5] Until FDA inspected the JSP manufacturing facility and evaluated multiple lots and samples of Unithroid as part of its review of JSP's NDA, the Agency could not establish that the JSP product satisfied the USP manufacturing standards, FDA's current good manufacturing practice requirements, or the criteria for NDA approval. Therefore, the pre-NDA sample of Unithroid used as the reference material for Mylan's ANDA 76-187 could not constitute an "appropriate reference material" as interpreted by FDA. The Mylan ANDA must, therefore, be revoked.

ACTIONS REQUESTED

We respectfully request that you withdraw approval of ANDA 76-187 submitted by Mylan Pharmaceuticals, Inc. for a generic Unithroid and request that it provide data based on a post-NDA sample of Unithroid.

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1 *Minutes of Jan. 23, 2004 Formal Dispute Resolution Meeting with Office of New Drugs*, Sec. C. 1. (Attachment A)

2 *Id.*

3 21 C.F.R. §§320.25 and 320.26.

4 *Id.* at §320.25((e)(3).

5 Containing less than 97 percent and not more than 103.0 percent of levothyroxine sodium calculated on the anhydrous basis. *See USP Official Monographs*, p. 1084.

STATEMENT OF GROUNDS

I. Background

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine (T4). Thyroid hormones affect protein, lipid, and carbohydrate metabolism; growth; and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production. The hormones possess a cardiostimulatory effect that may be the result of a direct action on the heart.

Orally administered levothyroxine sodium has been used for over 40 years as replacement therapy in conditions such as cretinism, myxedema, nontoxic goiter, and hypothyroidism. These conditions are characterized by a diminished or absent thyroid function. They may result from functional deficiency, primary atrophy, partial or complete absence of the thyroid gland, or the effects of surgery, radiation, or antithyroid agents. Levothyroxine is also used for replacement or supplemental therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism. In addition, the drug is used to suppress the secretion of thyrotropin in the management of simple nonendemic goiter, chronic lymphocytic thyroiditis, and thyroid cancer. Levothyroxine is also used with antithyroid agents in the treatment of thyrotoxicosis to prevent goitrogenesis and hypothyroidism.

Thyroid replacement therapy requires that the dosage be established for each patient individually. The initial dose is typically small and is increased gradually until a clinically optimal response is achieved; thereby the appropriate dosage maintenance level is established. The initial dosage and the rate at which the dosage may be increased is determined by the age and general physical condition of the patient and the severity and duration of hypothyroid symptoms.

FDA recognized that:

> "[i]t is particularly important to increase the dose very gradually in patients with myxedema or cardiovascular disease to prevent precipitation of angina, myocardial infarction, or stroke. If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on one product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestations of hyperthyroidism such as cardiac pain, palpitations, or cardiac arrhythmias. In patients with coronary heart disease, *even a small increase in the dose of levothyroxine sodium may be hazardous*. * * * Because of the risks associated with over treatment or under treatment with levothyroxine sodium, *it is critical that patients have available to them products that are consistent in potency and bioavailability*.[6]

II. The Approval of Oral Levothyroxine Products

On August 14, 1997, FDA issued a *Federal Register* notice calling for the submission of new drug applications for levothyroxine products.[7] Because levothyroxine products were

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6 62 *Fed. Reg.* 43535, 43536 (Aug. 14, 1997).

7 *Id.*

marketed in as many as 11 dosage strengths, which varied by only 12 µg, FDA recognized that variations in the amount of available active drug could affect both safety and effectiveness. In addition, FDA noted that the drug substance levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity. To address these concerns, FDA required § 505(b)(2) applicants to demonstrate that the various dosages they manufactured were dosage form equivalent.

> * * * *Unless the manufacturing process can be carefully and consistently controlled, orally administered levothyroxine sodium products may not be fully potent through the labeled expiration date, or* <u>*be of consistent potency from lot to lot*</u>. There is evidence from recalls, adverse drug experience reports, and inspection reports that *even when a physician consistently prescribes the same brand* of orally administered levothyroxine sodium, *patients may receive products of variable potency at a given dose*. Such variations in product potency present actual safety and effectiveness concerns. * * * Accordingly, any orally administered drug product containing levothyroxine sodium is a new drug under section 201(p) of the act (21 U.S.C. 321(p)) and is subject to the requirements of section 505 of the act. Manufacturers who wish to continue to market orally administered levothyroxine sodium products must submit [new drug] applications as required by section 505 of the act and part 314 (21 CFR part 314). * * * A bioavailability study must be completed and submitted as part of an NDA, including a 505(b)(2) application, *in order to evaluate the safety and efficacy of these products.* [8]

III. FDA Approval of JSP NDA for Unithroid

On August 22, 2000, FDA approved a NDA under §505(b)(2) for Unithroid. The application had been submitted to FDA on October 19, 1999. JSP was the first company to submit the application in response to FDA's Notice on August 14, 1997. The Agency provided that orally administered levothyroxine drug products must be subject to an approved NDA no later than August 14, 2000 because of expressed concerns about stability and potency of existing unapproved products.[9] Those products could be marketed only under an approved NDA unless FDA granted a specific exemption. That deadline for NDA approval was later extended one year until August 14, 2001.[10] In July 2001, FDA issued a Guidance document stating that if an application for approval of levothyroxine was not pending at FDA on August 14, 2001, distribution would have to be curtailed on a pro-rata basis.[11] JSP's Unithroid was initially listed in the *Orange Book* as the reference listed drug. Since levothyroxine was an older DESI drug,

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8 *Id.* (emphasis added).

9 *Supra* at note 6. Levothyroxine sodium has been marketed for over 40 years and was classified as a DESI product (Drug Efficacy Study Implementation).

10 62 *Fed. Reg.* 24488 (Apr. 26, 2000).

11 *Guidance for Industry, Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications*, July 2001, p.2-3, www.fda.gov/cder/guidance/4647/fnl.htm.

no patent was in-force which precluded generic competition. Therefore, once the NDA was approved and listed, a company was free to test samples of the approved Unithroid product and seek generic equivalence under an Abbreviated New Drug Application (ANDA).

IV. FDA Review and Approval of ANDA for Mylan Generic Levothyroxine

Mylan reportedly filed an ANDA on June 5, 2001 seeking to be approved as bioequivalent to Unithroid pursuant to §505(j). The ANDA was amended to address FDA questions and comments on November 7, 2001, November 12, 2001, January 18, 2002 and April 19, 2002. It was ultimately approved on June 5, 2002 in 11 strengths (Attachment B).

It is uncontested that the samples of Unithroid tested by Mylan were obtained from lots manufactured prior to approval of JSP's NDA on August 22, 2000. The record of the Mylan ANDA review available on FDA's website indicated that the FDA reviewers in the Office of Generic Drugs (OGD) were aware of the pre-NDA samples that were the basis of Mylan's bioequivalency analysis. Specifically, in an e-mail dated December 29, 2000, Donald Hare, acknowledged the "concern" of Gary Buehler, OGD Director, of "the formulation of the JS L/T tablets that were approved and the formulation of the JS L/T tablets that were being marketed without an approved application possibly not being the same" (Attachment C). Hare suggested that "[a]lthough the formulation of the two L/T tablets are probably the same I think it will have to be checked out." It was also pointed out that Mylan did three bioequivalence studies but did not use the same lot.

A follow-up e-mail from Mr. Buehler to Mr. Hare dated January 2, 2001, stated that "[s]ince there were no clinical trials required for this application, the feeling was that there may be some statement made that they have been marketing this same formulation for __ years etc." (Attachment D). The e-mail responded to a reported conversation between Chris Rogers and Mr. Hare in which it was suggested that historical data submitted with the JSP NDA could be used to answer the question of whether the Mylan NDA used the correct formulation in its BE study.

Finally, in an e-mail dated January 4, 2001, Mr. Hare reported to Mr. Buehler that FDA could not find any reference to a pre-approval formulation in JSP's NDA (Attachment E). However, David Lewis called his contact at JSP to confirm that JSP was marketing levothyroxine tablets before approval and whether the formulation was the same as what was approved. An unnamed contact at JSP reportedly indicated that the formulation "had not changed from the formulation that was marketed before approval." Hare stated that "[w]ith this information David did not have to ask additional questions to confirm what we hope to be true i.e. Mylan had used JS approved formulation in their BE study." The parties did not evaluate whether FDA's bioequivalency regulations deemed a pre-approval sample to constitute an appropriate reference material.

V. Use of Pre-Approval Sample by Mylan Could not Support ANDA Approval

FDA has consistently taken the position that the "Code of Federal Regulations requires that the reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application."[12] That legal conclusion is generally based on the Agency's interpretation of 21 C.F.R. §§320.25 and 320.26 "Guidelines for the conduct of an in vivo bioavailability study and single dose in vivo bioavilability study." Those regulations provide that "in vivo bioavailability testing of a drug product shall be in comparison to an appropriate reference material unless some other approach is more appropriate for valid scientific reasons."[13] It is provided that "the reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application and that contains the same active drug ingredient or therapeutic moiety..."[14]

FDA has also relied on a requirement that "pharmaceutical equivalence," in addition to bioequivalence, of two drug products must be established in order to obtain AB rating between the two drug products.[15] According to Dr. Jenkins and FDA lawyers, "pharmaceutical equivalence requires, among other things, a demonstration that the test and reference products contain the same amount of drug substance and that the two products are the same dosage form."[16] FDA bioequivalency regulations define "pharmaceutical equivalents" to mean "drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient."[17]

Given this interpretation of what sample constitutes an "appropriate reference material," the pre-approval samples of Unithroid taken from multiple lots cannot support approval of Mylan's ANDA. First, the Unithroid samples were not taken from a current batch of an approved drug product. The samples were taken from batches manufactured prior to approval of JSP's NDA.

Second, the pre-approval batches did not contain identical amounts of the identical active drug ingredient. They are, therefore, not pharmaceutical equivalents. As FDA is well aware, levothyroxine is an unstable ingredient that varies dramatically in potency. That is why FDA initially requested NDAs for this DESI product. That is also why even the USP manufacturing specification includes a range of 97 percent to 103 percent of the active ingredient. JSP adds an overage to the 100 percent active target in manufacturing. While JSP's formulation is more stable than its competitors, each lot of the drug varies in the level of potency at time of release, and those levels decline over time. Until JSP's NDA was reviewed, and its manufacturing establishment was inspected thoroughly, FDA could not verify that a reference material used in Mylan's application was "appropriate" and "pharmaceutically equivalent" for purposes of

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12 Letter from Dr. David G. Orloff, M.D. to JSP dated May 13, 2003 refusing to file JSP's supplement to its NDA seeking bioequivalence to Synthroid (Attachment F).

13 *Id.* at 320.25(c) and 320.26(a).

14 *Id* at §320.25(e)(3).

15 *Supra* note 1.

16 *Id.* at p. 2, section C.1.

17 §320.1(c).

determining bioequivalence and bioavailability. It was an impermissible short cut for personnel in OGD to ignore the bioequivalency regulations, or be unaware of them, and to simply call a contact at JSP to ask whether JSP's formulation had changed.

Finally, it would constitute the very definition of illegal "arbitrary" action by FDA to continue to honor Mylan's ANDA approval based on pre-approval Unithroid, but refuse to file JSP's application based on a pre-approval sample of Synthroid. It is not sufficient to differentiate Synthroid from Unithroid, in light of these regulations, by arguing that pre-approval lots of Synthroid may have contained a greater overage in the active ingredient. The scientific truth is that all levothyroxine degrades and that as long as the samples tested approximate the potency of the reference drug, the respective products cannot be distinguished based on overage.

Unless FDA withdraws Mylan's ANDA approval and treats the pre-approval samples of Unithroid and Synthroid in a consistent manner, FDA's action is by definition "arbitrary, capricious, an abuse of discretion, and not in accordance with the law," in violation of the Administrative Procedure Act.[18] The decision to approve the Mylan application when OGD realized its data was based on pre-approval samples of Unithroid was plainly wrong on the merits. It constituted improper *ad hoc* decision-making for OGD to resolve this issue by calling JSP to "confirm what we hope to be true,"or by not applying the bioequivlence requirements to Mylan, while applying them to JSP. The D.C. Circuit recently reiterated that "the core concern underlying the prohibition of arbitrary or capricious agency action is that agency 'ad hocery' is impermissible."[19]

VI. Mylan ANDA should be Withdrawn

The criteria requiring withdrawal of an approved ANDA are included in 21 C.F.R. §150. Among those criteria is a situation in which "the applicant has failed to submit bioavailability or bioequivalence data required under part 320 of this chapter."[20] As noted above, §§ 320.25 and 320.26 have been interpreted to require a reference material taken from a post-approval batch of Unithroid.

The procedure used to notify Mylan of FDA's decision in this matter is included in §314.151. It includes published notice and an opportunity to comment or request a hearing. Withdrawal of the Mylan ANDA until the proper post-approval reference sample can be tested will achieve FDA's interest in consistent non-arbitrary decision-making. It will also establish the precedent that post-approval batches constitute the appropriate reference material for future NDA and ANDA review.

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18 5 U.S.C. §706(a)(2).

19 *Ramaprakash v. Federal Aviation Administration*, 346 F.3d 1121, 1130 (D.C. Cir. 2003)(quoting *Pacific N.W. Newspaper Guild, Local 82 v. NLRB*, 877 F.2d 998, 1003 (D.C. Cir. 1989)).

20 21 C.F.R. §314.150(b)(5).

VII. Conclusion

Scientific standards for ensuring potency and stability and, therefore, safety and efficacy, for the labeled uses of levothyroxine sodium products, as well as the legal requirements for ensuring that a generic drug is the same as a reference listed drug, require that FDA immediately withdraw approval of the Mylan ANDA for levothyroxine until Mylan can provide a legally sufficient bioequivalency study based on a pharmaceutically equivalent post-approval sample of Unithroid.

ENVIRONMENTAL IMPACT

This petition is entitled to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

ECONOMIC IMPACT

Information regarding economic impact will be submitted on request.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

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A

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 23, 2004
TIME: 8:30 am to 10:00 am
LOCATION: Rockwall Room 1033, 5515 Security Lane, Rockville, MD
APPLICATION: NDA 21-210/S-003; Unithroid® (levothyroxine sodium tablets, USP)
TYPE OF MEETING: Formal Dispute Resolution (Refuse-to-File Appeal)
MEETING CHAIR: John K. Jenkins, M.D.
MEETING RECORDER: James T. Cross, M.S.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
John Jenkins, M.D.	Director	FDA/OND (HFD-020)
Warren Rumble	Ombudsman	FDA/OEP (HFD-006)
Robert Temple, M.D.	Associate Director	FDA/OMP (HFD-040)
Jane Axelrad, J.D.	Associate Director	FDA/ORP (HFD-005)
Gary Buehler	Director	FDA/OGD (HFD-600)
Robert Meyer, M.D.	Director	FDA/OND/ODE-II (HFD-102)
David Orloff, M.D.	Director	FDA/OND/DMEDP (HFD-510)
Dale Conner, Ph.D.	Team Leader	FDA/OGD (HFD-650)
Keven Fain, J.D.	Regulatory Counsel	FDA/OC/OCC (GCF-1)
Laurie Lenkel, J.D.	Regulatory Counsel	FDA/OC (HF-7)
James Cross, M.D.	Regulatory Project Manager	FDA/OND (HFD-020)

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
Jerome Steinlauf	President	Jerome Stevens Pharmaceuticals
Ronald Steinlauf	Vice President	Jerome Stevens Pharmaceuticals
Jake Thiessen, Ph.D.	Professor & Associate Dean	Faculty of Pharmacy, University of Toronto
Betty Cory	Vice President	PDi Regulatory Services
Marc J. Scheineson, Esq.	Partner	Reed Smith, LLP
Areta Kupchyk, Esq.	Counsel	Reed Smith, LLP
William Schultz, Esq.	Partner	Zuckerman, Spader

BACKGROUND:
NDA 21-210/S-003, submitted March 26, 2003, for Unithroid (levothyroxine sodium tablets, USP) proposed to establish that Unithroid is comparable (i.e., therapeutically equivalent) to Synthroid (levothyroxine sodium, USP) manufactured by Abbott Laboratories. This supplemental NDA requested an "AB" rating in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (referred to as the "Orange Book").

NDA 21-210/S-003

In a letter dated May 13, 2003, the Division of Metabolic and Endocrine Drug Products refused to file (RTF) the supplemental application under 21 CFR 320.25(e)(3), because the Synthroid reference material (Lot # 0000339726) was not the subject of an approved new drug application. JSP's response, dated May 23, 2003, requested a meeting and appealed the RTF decision to the Office of Drug Evaluation II (ODE II). Submissions to FDA's Office of Chief Counsel dated June 30, July 23 and 25, 2003, were also received and considered in the ODE II's October 3, 2003, correspondence, which upheld the Division's RTF decision.

On November 20, 2003, JSP requested reconsideration by the OND Immediate Office of the Division's RTF decision and the subsequent affirmation by ODE-II. In response, the OND immediate office (OND-IO) granted today's meeting with JSP in a letter December 19, 2003. A background package was submitted January 20, 2004, received January 21, 2004, for today's meeting.

MEETING OBJECTIVES:

1. For JSP to present their evidence and rationale as to why the Agency's refuse-to-file (RTF) action was incorrect.
2. For FDA to better understand the sponsor's views regarding the issues in dispute prior to making a decision on the Formal Dispute Resolution.

DISCUSSION POINTS:

After introductions, the Office of New Drugs (OND) explained that the Office of Medical Policy, to which JSP had directed the November 20, 2003, meeting request, was not the deciding office for appeals of a refuse-to-file (RTF) action. OND is the deciding office. OND also noted that no decisions would be made on the Formal Dispute Resolution Request (FDRR) at the meeting. OND stated that, following the meeting, it will consult internally on the scientific, regulatory, and legal issues prior to reaching a decision on the FDRR. That decision will then be communicated to the sponsor in a letter.

Two presentations, one scientific and one regulatory, were given by Jerome Stevens Pharmaceuticals, Inc. to explain why the company believes that the Agency's decision to RTF the application was incorrect. Following the presentations, a discussion of the issues related to the RTF decision and the request for dispute resolution was held between JSP and FDA staff. A brief summary of some of those issues is captured below.

A. Scientific Presentation on Unithroid

JSP affirmed that tablets from a marketed pre-approval batch of Synthroid were used as the reference material for their bioequivalence study. Dr. Thiessen's presentation addressed three scientific issues regarding the RTF decision related to the use of pre-approval Synthroid: (1) differences between pre- and post- approval Synthroid, (2) levothyroxine overage, and (3) degradants. Slides of this presentation are appended for reference.

B. Regulatory/Legal Presentation on Unithroid

The purpose of this presentation, according to JSP, was two-fold: (1) to provide an understanding of the basis for the RTF decision and (2) explain why the reference material used by JSP in their

bioequivalence trial should be considered acceptable. Slides of this presentation are appended for reference.

C. Sponsor/Agency Discussion

1. **AB Rating:** Following the two presentations, the Agency stated that pharmaceutical equivalence and bioequivalence of two drug products must be established to in order to obtain an AB rating between those two drug products. Pharmaceutical equivalence requires, among other things, a demonstration that the test and reference products contain the same amount of drug substance and that the two products are the same dosage form. The Agency noted that the pre-approval batches of Synthroid were released with a stability overage and that this overage draws into question whether the two products are pharmaceutical equivalents. On behalf of the sponsor, Dr. Thiessen responded that bioequivalence is a test of dosage form performance and that potency correction can account for overage provided that the two products are within the same range of potency. He also noted that at the time of use in the bioequivalence study that the tablets of pre-approval Synthroid were assayed and contained an amount of drug substance very close to the labeled dose. He concluded that the results of the bioequivalence test were therefore informative for how Unithroid would perform in comparison to tablets from a post approval batch of Synthroid, which do not contain a stability overage.

2. **Degradation/Overage:** The Agency noted that the sponsor was using the fact that levothyroxine degrades over time as a substitute for using pharmaceutically equivalent products in the bioequivalence assay. The Agency noted that stability overages are not allowed for any of the approved levothyroxine products. The Agency reiterated that formulations of new drugs are defined not simply by the list of ingredients, but also by the amount of the drug substance in the product. The Agency has concluded that because of the presence of a stability overage pre-approval and post-approval Synthroid tablets are not pharmaceutically equivalent. JSP countered that FDA did not require a bridging study between pre-approval and post-approval Synthroid and that the Agency did not require re-titration of patients who had previously been treated with pre-approval Synthroid once Synthroid was approved. JSP also noted that the agency had granted an AB rating to Mylan Pharmaceuticals' ANDA levothyroxine product based on a comparison to pre-approval Unithroid. JSP argued that this suggested that a pre-approval product could be used to support an AB rating.

3. **Trial Design:** The Agency asked the sponsor to specify what issues JSP had sought input on from FDA when designing their bioequivalence trial. JSP stated that they had received general guidance regarding study design but that they had not submitted a detailed protocol to the Agency for review. The Agency specifically asked if JSP had ever contacted the Agency about what constituted an appropriate reference material, i.e., whether pre-approval product would be considered an appropriate reference material. In response, JSP stated that it never sought FDA input on what would be an appropriate reference product. JSP stated that their decision to use tablets from a pre-approval batch of Synthroid for the bioequivalence study was based on the fact that they were unable to purchase Synthroid tablets from a post-approval batch. JSP felt that they could not continue to wait until Synthroid tablets from a post-approval batch were commercially available. JSP also stated that they assumed that tablets from a pre-approval batch would be acceptable since the Agency did not make any public statements that led the firm to believe that their selection of pre-approval product would be unacceptable as a reference.

NDA 21-210/S-003

4. **Regulatory Requirements for Establishing Bioequivalence:**
   - The Agency and the sponsor discussed the specific citations from the Code of Federal Regulations that had been cited by the Agency as justification for its RTF decision as well as other applicable regulations and Agency guidance documents as they relate to the issue of the selection of an appropriate reference material. JSP argued that, as written, the regulations allowed for Agency flexibility in determining an appropriate reference material and argued that they had provided adequate scientific data to support their view that the pre-approval Synthroid was an appropriate reference material.

The Agency concluded the meeting with a reminder to the sponsor that they should not have introduced new data during the meeting. The Agency noted that, as described in the guidance for industry entitled, *Formal Meetings With Sponsors and Applicants for PDUFA Products*, no new information should be submitted as part of the reconsideration request or appeal. Lastly, the Agency stated that a response to the request for formal dispute resolution would likely take more than 30 days from the meeting date since the Office of Chief Counsel was being solicited for input.

The Agency stated that, according to our procedures, a response to the request for formal dispute resolution would be completed within 30 days from the meeting date unless consultation with the Office of Chief Counsel was necessary, in which case additional time may be required. The Agency noted that given the issues raised by the sponsor in the FDRR it was likely that OCC consultation would be required prior to a final decision.

DECISIONS (AGREEMENTS) REACHED:
The Agency stated that it will respond to the request for formal dispute resolution dated November 20, 2003, after the Office of New Drugs has conferred with the Office of Chief Counsel.

ACTION ITEMS:

Item	Responsible Person	Due Date
Issue response to request for formal dispute resolution	John Jenkins, M.D.	30 days from date of dispute resolution meeting (more than 30 days may be needed when consulting FDA's Office of Chief Counsel)

Minutes Preparer: James Cross
Regulatory Project Manager

Chair Concurrence: *see appended electronic signature page*
John K. Jenkins, M.D.
Director, Office of New Drugs
Center for Drug Evaluation and Research

NDA 21-210/S-003

ATTACHMENTS/HANDOUTS:

1. Dr. Thiessen's presentation entitled, *A Scientific Perspective on the Bioequivalence of Unithroid and Synthroid.*
2. Areta Kupchyk's presentation entitled, *Unithroid-Synthroid Bioequivalency Legal/Regulatory Overview.*

cc: Original
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-020/RPM, ADRA, and Director
HFD-510/RPM and Attendees
HFD-102/Attendees
HFD-600/Reviewers & Attendees
HFD-005/Attendees
HF-007/Attendees
GCF-001/Attendees

Drafted by: J.Cross/1-26-04

Revised by: G.Buehler/1-27-04; L.Lenkel/1-30-04, 2/17/04; J.Axelrad/2-19-04; J.Cross/2-9-04, 2-20-04; R.Temple 2/18/04; J.Jenkins/2-19-04; K.Colangelo/2-20-04

Initialed by: D.Orloff/2-3-04

Final: J.Jenkins/2-20-04

MEETING MINUTES